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EXAMINER
PERKINS, S

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892. (2sheets) 2. ☑ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449. 4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474. 6. ☑ Requirements for Application containing Amino Acid Sequence

Part II SUMMARY OF ACTION

1. ☑ Claims 1-5 are pending in the application.
   Of the above, claims ____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 1-5 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☑ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

15. Claims 1-5 are pending in this application.

16. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."**

17. The specification is objected to and claims 1-5 are rejected to under 35 U.S.C. 112, first paragraph, as failing to adequately teach how to make and/or use the claimed invention, i.e. failing to provide an enabling disclosure.

The specification does not support the asserted and claimed utility of treating respiratory distress syndrome (RDS) with the compositions of interest. First, for most of species embraced by the generic formula, Applicants have only provided in vitro data. The only biological testing in rabbits is for surfactant polypeptides not embraced by the claims of this application. Moreover, for the preferred species, such as that of claim 5, there is not even in vitro data presented. There are no working examples set forth which demonstrate that a surfactant activity will be enhanced in vivo by using the claimed surfactant polypeptides. While Applicants assert that in vitro the surfactant activity is increased (Table 7) there is no evidence of record to demonstrate that a similar phenomenon would occur in vivo. While data obtained from in vitro assays are useful in screening for potentially therapeutic agents one cannot

simply extrapolate the data to in an in vivo system. The success of using the polypeptides to treat RDS is dependent upon a number of factors, such as the maturity of the fetus, successful delivery of the surfactant, and the ability of the particular surfactant specie to bind to lung epithelial cells, to name a few. Moreover, Applicants' claims embrace a large number of these polypeptides and said polypeptides can vary substantially in amino acid composition and length and say peptides may have little to no homology with native SP18.

Applicants' methods claims and the use of the polypeptides of interest is to treat respiratory distress syndrome, a disease associated with pre-term infants lacking sufficient pulmonary surfactant. One of the articles provided by Applicants in the parent application and made of record herein, Enhorning, discusses the procedures used by Applicants for testing their peptide in vitro. While it is clear that the procedures are readily available and present advantages for testing surfactant compositions over other existing methods, even Enhorning states that these procedures permit quick screening of a large number of samples (page 202, last paragraph). Enhorning does not comment on the extrapolation of the results obtained to in vivo utility, but rather only highlights that the procedures are useful for preliminary screening for possible surfactant candidates.

Applicants supplied three references in the parent application, which have been made of record herein, in support of the teachings of the specification as being enabling for the use of the instant polypeptides. As discussed above the article by Enhorning sets forth the procedures for an in vitro test, indicates that such is a good method for screening a large number of surfactants, and does not set forth that the results obtained with

the procedures can be used as a reliable and predictive tool for what will occur in vivo. The other two references provided by Applicants have both in vitro and in vivo data. In fact the article to Revak et al. seems to set forth that there are compelling reasons for doing both in vitro and in vivo studies; "there is a necessity to correlate the surface activity properties of decreased surface tension and rapid absorption of reconstituted surfactant mixtures with their physiologic activity in pulmonary mechanics. For these reasons, we assessed surface activity both in vitro... and in vivo.." (page 1285, second column). As stated above, many of the peptides of interest have not been tested in vivo, and in particular not the preferred species ~~of claims 18 and 88~~. This is despite the fact that those of skill in the art (i.e. the inventors) seem to present reasons why such is quite useful and necessary for assessing a polypeptides ability to serve as a useful pulmonary surfactant. The article to Suzuki et al. also presents both in vitro and in vivo data. Suzuki et al. reference an article by Nohara et al. which seems to indicate that "the in vitro properties of surfactant preparations do not necessarily predict the in vivo effects.." (page 344, first full paragraph). Moreover the article to Suzuki et al. reports that the apoprotien-based material tested by them had similar activity as that of natural surfactant, and yet Suzuki et al. state that "these promising results should encourage systematic experimental work" on the same 15,000-dalton apoprotein as tested by them.

If the utility of an invention is for purposes of treating humans, such as treating RDS, evidence of utility must generally be clinical evidence. See MPEP 608.01(p). This would especially be true where such treatment is multifactorial and unpredictable, as is with this vulnerable disease state. Also the peptide art is unpredictable, particularly where the compositions include

polypeptides which can vary in composition and length. Many of the peptides which fall within the claims and in particular the preferred peptides, have not been tested even in vivo in any another mammalian specie, much less in humans. While animal data may be sufficient, the critical issue would be whether or not the testing procedures utilized are recognized by the skilled generally as being reasonably predictive of success in the ultimate intended utility. The resolution of this issue is closely dependent on the facts of each case. In re Jolles, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); Nelson v. Bowler, 626 F. 2d 853, 206 USPQ 881 (CCPA 1980); In re Buting, 418 F.2d 540, 163 USPQ 689 (CCPA 1969); Ex parte Busse, 1 USPQ2d 1908 (BPAI 1986). In the instant case there has been no convincing evidence set forth that such testing procedures as the in vitro pulsating bubble technique or lung static compliance in fetal rabbit are sufficiently predictable as to what will occur in vivo in humans concerning such a disease as RDS. In fact the evidence indicates the contrary. The pulsating bubble technique is reported as being useful for screening. And in the other articles, presented both in vitro and in vivo data is presented, and reasons for doing both are set forth, one article reports that in vitro properties of surfactant preparations do not necessarily predict the in vivo effects and it further reports that despite the surfactant preparation having similar activity as natural surfactant, more testing would be useful.

18. The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> **"A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the**

prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person."

19. Claims 1 and 3 are rejected under 35 U.S.C. 103 as being unpatentable over Jackson ('756).

Jackson discloses surfactant polypeptide which have alternating hydrophilic and hydrophobic amino acid regions. A number of surfactant peptides embraced by Applicants' generic formula are encompassed by the generic formula taught by Jackson. See especially col. 2, Formula 1 and col. 3, lines 46-68. See also that T_N can be T_N· which is hydrogen, an amino acid, or a dipeptide and that nearly any position of Jackson can be Tyr (one of Applicants' "U" amino acids). Jackson teaches that by alternating the hydrophobic and hydrophilic amino acids the amphipathic molecules have a helical conformation and that such structure is associated with interactions with phospholipid and surfactant activity. One would be motivated to prepare the polypeptides embraced Jackson's generic formula based on the expectation of structure and function, mainly surfactant activity and proper interaction with phospholipid based on alternating hydrophobic and hydrophilic regions.

It should be noted that while Jackson's generic formula embraces peptides that are also embraced by Applicants' generic claims, the patent does not anticipate the instant claims and the peptides embraced thereby. The description of "specific preferences

in connection with a generic formula" is determinative on an analysis of anticipation under 35 U.S.C. §102. In re Petering, 301 F.2d 676,133 USPQ 275, 279(CCPA 1962), Merck & CO. Inc. v. Biocraft Laboratories Inc., 10 USPQ2d 1843, 1846 (CAFC 1989). Jackson disclosed certain preferences for the composition of the surfactant protein at col. 3, lines 52-56. Considering these preferences, the Jackson patent does not anticipate the instantly claimed subject matter. According to the preferences recited in col. 3, there would never be a polypeptide having at least three hydrophobic amino acids conjugated together which is essential to the compounds of the instant application (i.e. U_{3-20}).

In a section 103 inquiry, "the fact that a specific [embodiment] is taught to be preferred is not controlling, since all the disclosures of the prior art, including unpreferred embodiments, must be considered". In re Lamberti, 545 F.2d 747, 750, 192 USPQ 278, 280 (CCPA 1976). Merck & CO. Inc. v. Biocraft Laboratories Inc., 10 USPQ2d 1843, 1846 (CAFC 1989). For an analysis of Applicants' claims under §103 the disclosure of Formula 1 at col. 2 is pertinent. See Merck & CO. Inc. v. Biocraft Laboratories Inc. for a discussion of where a prior art patent which teaches a genus and instructs an artisan of 1,200 combinations renders obvious one single combination even though the prior art reference does not highlight this combination.

20. Claims 1-5 are provisionally rejected under the judicially created doctrine of double patenting as being unpatentable over claims 17, 18, 31, 33, and 35-39 of copending application Serial No. 07/293,201. Although the conflicting claims are not identical, they are not patentably distinct from each other because there is an overlap in scope in what is being claimed in the conflicting claims of these applications. The generic claims of each of these

applications overlap in scope and cover many of the same peptide species. The only difference between the generic claims is that in this application Z is only Arg and Lys and not Arg. Lys. Glu. and Asp, which is Z in the other pending application. However, even with this more limiting scope, many of the surfactant polypeptides falling with in the generic claims of the other pending application would also be embraced by the generic claims of the instant application. Moreover, the species claims of the instant application, which concern the specie KLLLLKLLLLKLLLLKLLLLK, would be embraced by the generic claims of 07/293,201 application. For, these reasons the conflicting claims overlap in scope. Applicants may not extend their exclusionary interest by taking out claims of overlapping scope in two separate patent applications. Applicants must file a terminal disclaimer.

This is a provisional double patenting rejection because the conflicting claims have not in fact been patented.

21. The double patenting rejection is a judicially established doctrine based upon public policy and is primarily intended to prevent prolongation of the patent term by prohibiting claims in a second patent not patentably distinct from claims in a first patent. *In re Vogel,* 164 USPQ 619 (CCPA 1970). A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) would overcome an actual or provisional rejection on this ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. § 1.78(d).

22. The specification is objected to under 37 CFR §1.821 through §1.825. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR §1.821(a)(1) and (a)(2). However, this application does not comply with the requirements of the regulations. The application fails to comply with the collective requirements of 37 CFR §1.821 through §1.825. Applicant's attention is directed to these regulations, a copy of which is attached.

Applicant does not benefit from the parent application's filing date to obviate complying with these regulations to the extent that any new peptide specie(s) are specifically disclosed in this application that was not specifically disclosed in the parent application. One specie, for example, that was not specifically disclosed in the parent application, as far as the examiner can see, is the polypeptide KLLLLKLLLLKLLLLKLLLLK. This polypeptide is now the subject of claims 2, 4, and 5 of the instant application. Also there are peptide species in Table 3 that the examiner does not see as being specifically disclosed in the parent application. Applicant must either point out where these peptides were specifically disclosed in the parent application or Applicant must comply with the sequence requirements of 37 CFR §1.821 through §1.825 regarding the amino acid sequences now specifically disclosed that were not specifically disclosed in the parent application.

23. The art cited but not relied upon is related to the nature of the application.

24. Claims 2, 4, and 5 are free of the prior art. The prior art does not teach or suggest the particular surfactant polypeptide of these claims, KLLLLKLLLLKLLLLKLLLLK. Jackson does not teach surfactant polypeptides which have stretches of leucine as Applicants' specie has.

25. No claims are allowed.

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Susan Perkins whose telephone number is (703)-308-1030. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703)-308-0196.

S.M. Perkins
09-25-91

JOHN DOLL
SUPERVISORY PATENT EXAMINER
ART UNIT 189B